# Diverse Brain Tumor Subtypes Have an Unanticipated Common Origin

October 20, 2014

A Neves

Glioblastomas (GBMs) are the most common and deadly form of brain cancer. GBMs can be divided into two classes, based on the levels of a chemical tag called methylation (Noushmehr et al., 2010). In addition, gene expression profiling has subdivided GBMs into four subtypes: Classical (CLS), Proneural (PN), Neural (NL), and Mesenchymal (MES) (Verhaak et al., 2010). However, the clinical relevance of these subtypes, and whether they originate from a common precursor, had remained unclear.

To address these important questions, Staff Scientist Dr. Tatsuya Ozawa and colleagues in the lab of Dr. Eric Holland (Human Biology Division and Solid Tumor Translational Research) and their collaborators, combined mathematical and tumor modeling techniques to retrace the evolutionary steps that occurred within or across subtypes, as well as to ascertain the biological relevance of such steps in mouse GBM models.

To investigate the nature and frequencies of genomic alterations in the GBM subclass with low levels of methylation (non-glioma-CpG island methylator phenotype; non-GCIMP), the authors mined data from The Cancer Genome Atlas (TCGA), a public repository of cancer genomes. Strikingly, the authors found that a gain of several copies of chromosome (chr) 7 and a loss of one copy of chr 10 were by far the most frequent events in all non-GCIMP GBMs. To determine the temporal sequence of genomic alterations in GBM, the researchers used a computational method called Retracing Evolutionary Steps in Cancer (RESIC). Application of the RESIC algorithm to the TCGA data revealed that broad copy number alterations in chr 7 and chr 10 were the first events in all non-GCIMP GBM subtypes. Subsequently, loss of the tumor suppressors *CDKN2A* and *TP53* occurred, while alterations that preferentially occur in each subtype were surprisingly late events. " These findings suggest that acquisition of multiple pro-oncogenic alterations by copy number gain or loss at the outset of tumor formation may reduce the likelihood of success of targeted therapies against subtype-specific events, " said Dr. Ozawa.

Next, the authors searched for drivers of tumor development in chr 7 gain and chr 10 loss. By computationally ranking genes based on the correlation between their expression levels, copy number gains, and association with patient outcome, the investigators found that *PDGFA* (chr 7) and *PTEN* (chr 10) were the strongest, but not the only, driver events. To validate these predictions with mouse models, the authors used a system that allows post-natal, cell type-specific gene transfer to express high levels of human PDGFA in Nestin- or GFAP-expressing cells of the mouse brain. These modeling experiments showed that elevated PDGFA expression was sufficient to induce gliomas *in vivo*. Loss of the tumor suppressor *PTEN* alone was insufficient for gliomagenesis, but it markedly enhanced PDGFA-induced gliomas, decreasing the median survival time. Similar enhancement of PDGFA-induced gliomas was observed by depleting the tumor suppressors *CDKN2A* or *TP53,* which are frequently lost in human GBM.

Further mathematical models predicted that the primordial gliomas driven by broad copy number alterations were proneural in character, with the other subtypes evolving from them. Therefore, the authors determined whether loss of the tumor suppressor*NF1*, a characteristic mutation of the mesenchymal subtype of GBM, could convert proneural GBMs to mesenchymal GBMs in mice. Indeed, they showed that loss of NF1 shifted PDGFA-induced gliomas from a proneural to a mesenchymal character, both by histological and expression profiling criteria.

While these studies suggest that elevated expression of *PDGFA* and reduced expression of *PTEN* are the primary drivers for chr 7 gain and chr 10 loss, respectively, the authors point out that other genes residing on these chromosomes could contribute to oncogenesis and may make precision inhibition of any specific target less effective. From the mechanistic standpoint, GBMs are distinct from chronic myelogenous leukemia, where the initiating event is the generation of a single oncogenic protein. Because most of the current therapeutic targets appear to be late events in GBM evolution," future studies should be aimed at identifying the common molecular events across all subtypes, which may be promising therapeutic targets", Dr. Ozawa explained.

Citation:

Ozawa T, Riester M, Cheng Y-K, Huse JT, Squatrito M, Helmy K, Charles N, Michor F, Holland EC. 2014. Most human non-GCIMP glioblastoma subtypes evolve from a common proneural-like precursor glioma. *Cancer Cell*. 26(2):288-300.

See also:

Noushmehr H, Weisenberger, D JDiefes K, Phillips HS, Pujara K, Berman BP, Pan F, Pelloski CE, Sulman EP, Bhat KP, Verhaak RG, Hoadley KA, Hayes DN, Perou CM, Schmidt HK, Ding L, Wilson RK, Van Den Berg D, Shen H, Bengtsson H, Neuvial P, Cope LM, Buckley J, Herman JG, Baylin SB, Laird PW, Aldape K, Cancer Genome Atlas Research Network. 2010. Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. *Cancer Cell*. 17(5): p. 510-22. PubMed Central PMCID: PMC2872684.

Verhaak RG, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, Miller CR, Ding L, Golub T, Mesirov JP, Alexe G, Lawrence M, O'Kelly M, Tamayo P, Weir BA, Gabriel S, Winckler W, Gupta S, Jakkula L, Feiler HS, Hodgson JG, James CD, Sarkaria JN, Brennan C, Kahn A, Spellman PT, Wilson RK, Speed TP, Gray JW, Meyerson M, Getz G, Perou CM, Hayes DN, Cancer Genome Atlas Research Network. 2010. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell*. 17(1): p. 98-110. PubMed Central PMCID: PMC2818769.

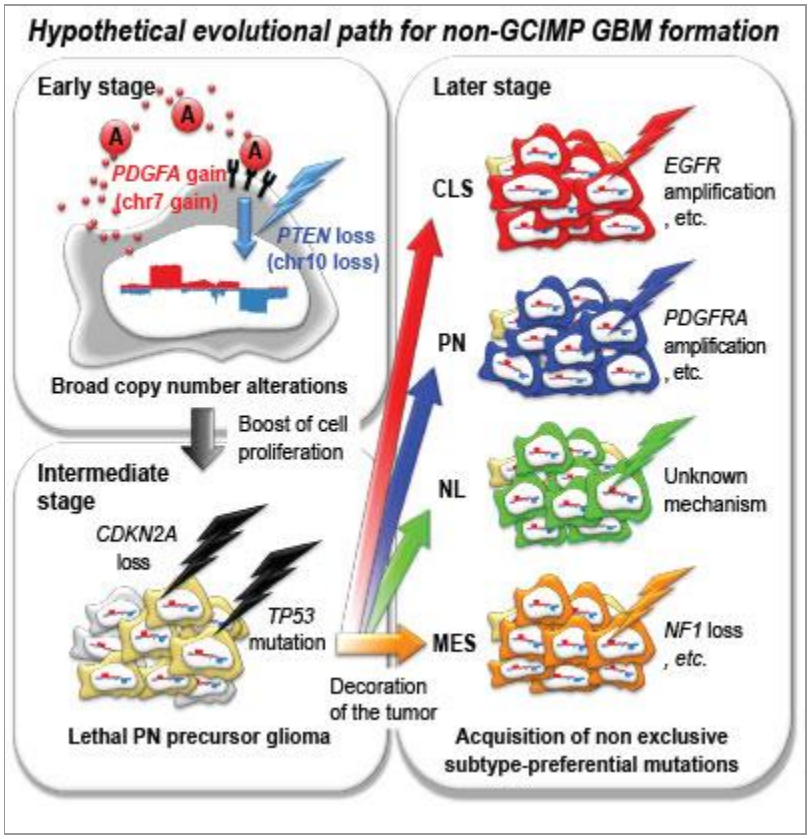


*Image provided by Dr. Ozawa*

Predicted evolutionary trajectory for non-glioma-CpG island methylator phenotype glioblastoma (non-GCIMP GBM). Broad copy number alterations in chromosome 7 and chromosome 10 appear to be the earliest events, which boosts proliferation of glioma precursors. Next, loss of the tumor suppressors CDKN2A and TP53 occurs. Finally, the proneural GBM precursor acquires subtype-enriched mutations, such as NF1 loss for the mesenchymal (mes) subtype.